REMARKS

Introduction

Applicant thanks Examiner Gupta and his supervisor, Examiner Brumback, the courtesies extended by them, during an interview with applicant's representative on February 26, 2003. The following remarks reflect the content of that interview.

Receipt is acknowledged of a final office action dated November 5, 2002. In the action, the examiner rejected claims 1-10, 16 and 18-44 for alleged nonenablement. The examiner, however, did not maintain his rejection of claims 7-9 for alleged indefiniteness and therefore, the rejection is deemed withdrawn.

Status of the Claims

In this amendment, applicant cancelled claims 11-15 and 17 for being drawn to a non-elected invention and added new claims 45-46. Support for new claims 45-46 can be found on page 5, lines 17-31 of the instant specification. Upon entry of this amendment, 1-10, 16, and 18-46 will be pending.

The present amendment does not necessitate a further search and does not raise new issues. Applicant respectfully requests entry of the amendment and reconsideration of the present rejection in light of the following remarks.

35 U.S.C. § 112, 1st paragraph

The examiner maintained his rejection of claims 1-10 and 16 and rejected newly added claims 18-44 for alleged non-enablement, indicating that there is unpredictability associated with structural changes and that the specification does not provide sufficient guidance for these changes to enable the breadth of the claims (office action at 6).

The specification provides sufficient guidance as to which IGF analogs are suitable for use in the present invention

In the action, the examiner asserted that the specification does not provide guidance as to which "of the 60 amino acids are not essential amino acids[, and therefore, which] may be substitute[d], retained[,] or deleted" (office action at 6). Applicant respectfully disagrees.

As stated in applicant's last response, null IGFs are well defined and a person of skill in the art would know which amino acids could be changed based on the regions identified as "critical" for IGF receptor and IGFBP binding. *See*, Jannson reference submitted with Paper No. 16. In addition,

references describing the state of the art regarding null IGF at the time of filing are submitted herewith. *See* Exhibit A. Furthermore, the specification describes that null IGFs of the present invention have a reduced affinity for the IGF receptor and a maintained ability to complex IGFBP-3. Exemplary null IGFs are also outlined on page 5 and example 2 of the application. Therefore, the specification adequately teaches a skilled artisan how to make and use the null IGFs of the present invention.

The examiner errs, as a matter of law, in requiring data showing clinical efficacy

Next, the examiner asserted that "[o]ne of ordinary skill in the art would have to determine the pharmokinetics [*sic*], such as drug absorption and drug clearance, of the analog before it could be utilized in the inhibition of tumor growth in an individual" (office action at 4). As a matter of law, however, this position is untenable. Efficacy for drugs is determined by the FDA, while enablement for a patent claim is determined by the PTO. "The Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs in the United States" (MPEP § 2107.01). Therefore, a failure to demonstrate the clinical efficacy of a drug in no way reflects a descriptive shortcoming in the application, let alone one that deprives the present claims of "enablement," within the meaning of § 112.

Similarly, the PTO also provides that "[o]ffice personnel should not impose on appellants the unnecessary burden of providing evidence from human clinical trials." M.P.E.P § 2107.02, Section IV. In other words, information that relates to a drug absorption and clearance, which is the focus of clinical trials, is not a legal criterion for enablement.

The examiner errs, as a matter of law, in requiring an "art recognized" animal model

Continuing, the examiner addressed the alleged limitations of animal models during the examiner interview and uses this as a basis for doubting the correlation between applicant's *in vivo* results and a human therapeutic effect of null IGFs. The examiner then provided two references (*Science*, 278:1041 (1997) and *Science*, 271:1079 (1996))) which purportedly diminish the significance of a PC-3 animal model. However, the theme underlying these publications is that "the future of cancer drug screening is turning almost exclusively toward defining molecular targets" (*Science*, 778:1042) and the present invention clearly highlights the molecular target as wild-type IGF. *See*, specification at 6 and declaration (Exhibit B) at paragraph 7.

Moreover, there is no per se requirement that an animal model used in a patent application to support a claim of biological activity must be demonstrated to be "art-recognized". Unless there are

specific reasons to doubt the correlation between a certain experimental animal and treatment of the disease condition itself, the evidence should be accepted as presumptively accurate. *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (CCPA 1971). For example, in *In re Langer*, 183 U.S.P.Q. 288 (CCPA 1974), the Court held that the evidence required to rebut a case of non-enablement or lack of utility established by the Examiner need only be sufficient to rebut the evidence presented by the Examiner. Thus, in *Langer*, 183 U.S.P.Q. at 297, applicants' evidence from an animal model, whether or not the animal model was "art-recognized", was more than sufficient to rebut the doubts raised by the in vitro data provided in the references cited by the Examiner.

In any event, it is sufficient to use a "standard experimental" animal, which was defined *in In re Krimmel,* 130 U.S.P.Q. 215, 219 (1961), as "whatever animal is usually used by those skilled in the art to establish the particular pharmaceutical application in question." See also, *In re Hartop*, 135 U.S.P.Q. 419 (1962). Therefore, applicant submits copies of abstracts that demonstrate that a PC-3 animal model is frequently used by one of skill in the art to determine the therapeutic utility of a particular drug. *See*, Exhibit C. Also, a declaration which is filed concurrently herewith attests to the relevance of the animal model used in the present invention ("as predicted from studies in the PC-3 animal model, a null IGF applied to any cancer associated with IGF-induced cellular proliferation would have an anti-cancer effect" (declaration at paragraph 8)).

The instant specification is enabling for treatment of a cancer, including prostate cancer

As indicated in the appended declaration, the null IGF technology of the present invention is suitable for treatment of a human cancer and is not limited to prostate cancer. See, declaration at paragraph 7. Although the PC-3 animal model is a prostate cancer model, the therapeutic utility of Y60L in the PC-3 xenograft can be extrapolated to support the utility of a null IGF in other cancers. Indeed, the relationship between IGFs and cancer risk has been well studied and null IGFs are therefore suitable for slowing the growth rate and/or progression of any cancer for which IGFs have been implicated. Abstracts implicating IGFs in cancer progression are provided in Exhibit D.

Computer modeling can predict the efficacy of a therapeutic agent

Continuing, the examiner stated that "computer modeling cannot sufficiently predict protein structure nor predict the efficacy of the therapeutic agent" (office action at 4-5). The examiner then provided several references which allegedly stand for the proposition that a determination of *in vivo* efficacy would require undue experimentation "since more work the [*sic*] simple routine assay[s] are required to determine if an analog would be effective in inhibiting tumor growth" (*id.* at 5). Applicant, however, respectfully contends that the examiner mischaracterized the cited publications.

For example, the 1992 *Science* article that the examiner presented indicates that it is not yet feasible to sit at a computer and design a drug from scratch" (*Science*, 256:441 (1992), emphasis added). As such, this article does not describe the feasibility of designing a null IGF *in silico* based on existing structural information. Indeed, this reference does not consider computer drug design when structural data is available. Since structural information for IGF existed at the time of filing, the structure of IGF analogs would not be predicted "from scratch."

Moreover, the *Science* article addresses the advantage of using computers in conjunction with experimentation and describes how Hopkins researchers successfully "alter[ed] the drug's biological potency by changing its chemical structure" and "use[d] supercomputers to see how the structural changes affect the interaction between cyclophosphamide's active metabolite...and DNA" (*id*). As such, the *Science* reference does not support the proposition that "computer models are not an effective method of determining drug activity" (office action at 5).

The facts in Amgen substantially differ from the facts in the instant case

To further support the examiner's contention of non-enablement, the examiner cited the Federal Circuit's holding in *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991). Applicant, however, respectfully asserts that the facts of *Amgen* cannot be applied to the instant application. Amgen claimed all possible genetic sequences with EPO-like activity (*i.e.*, polynucleotide sequences with an amino acid sequence "sufficiently duplicative" of EPO) after identifying the EPO gene and a few analogs with unknown activity. The number of species, however, that fall within the scope of sequences with EPO-like activity is tremendous. Indeed, the district court noted that "over 3,600 different EPO analogs can be made by substituting at only a single amino acid position and over a million different analogs can be made by substituting three amino acids" (*Amgen*, 927 F.2d at 1213). This is in sharp contrast to the null IGFs of the present invention. Not only have null IGFs been well defined in the art, they represent a very narrow subset of IGF analogs. Accordingly, it would not be reasonable to compare the facts of the instant case with *Amgen*.

CONCLUSION

Applicant submits that this application is in condition for allowance and solicits an early indication to that effect. Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, a telephone call to the undersigned is courteously invited.

Respectfully submitted,

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PENDING CLAIMS FOR "NULL IGF FOR THE TREATMENT OF CANCER"

AS OF MARCH 18, 2003 (F&L REF: 057491/0413)

1. (Amended) A method for slowing the growth rate of a tumor, comprising: administering an effective amount of uncomplexed null insulin-like growth factor I (IGF-I) to a subject having cancer.

2. The method of claim 1, wherein said cancer is selected from the group conssiting of breast, prostate, colon and lung cancer.

3. The method of claim 2, wherein said cancer is breast cancer.

4. The method of claim 2, wherein said cancer is prostate cancer.

5. The method of claim 2, wherein said cancer is colon cancer.

6. The method of claim 2, wherein said cancer is lung cancer.

7. (Amended) The method of claim 1, wherein the residue at position 60 of the amino acid sequence of said null IGF-I is altered to a non-aromatic residue.

8. (Amended) The method of claim 7, wherein the residue at position 24 or 31 of said amino acid sequence of said null IGF-I is additionally altered to a non-aromatic residue.

9. The method of claim 7, wherein said nulll IGF-I is additionally altered at a position selected from the group of positions 49, 50, 51, 53, 55 and 56.

10. The method of claim 1, wherein said null IGF-I is administered at about 0.01 to about 50 milligrams per kilogram total body weight per day (mg/kg/day).

Claims 11-15 were subject to a restriction requirement.

16. A method for slowing progression of a cancer comprising: administering an effective amount of uncomplexed null insulin-like growth factor I (IGF-I) to a subject having cancer, thereby slowing progression of the cancer.

Claim 17 was subject to a restriction requirement.

18. (New) The method of claim 1, wherein the residue at position 60 of the amino acid sequence of said null IGF-I is altered to a leucine residue.

19. (New) The method of claim 1, wherein the residue at position 24 of the amino acid sequence of said null IGF-I is a non-aromatic residue.

20. (New) The method of claim 19, wherein the residue at position 31 of said amino acid sequence of said null IGF-I is a non-aromatic residue.

21. (New) The method of claim 1, wherein the residues at positions of 24, 31 and 60 of the amino acid sequence of said null IGF-I are altered to a non-aromatic residue.

22. (New) The method of claim 1, wherein the amino acid sequence of said null IGF-I is altered such that residues 28 to 37 are replaced with four glycine residues.

23. (New) The method of claim 22, wherein the residue at position 60 of the amino acid sequence of said null IGF-I is a non-aromatic residue.

24. (New) The method of claim 22, wherein the residue at position 24 of the amino acid sequence of said null IGF-I is a non-aromatic residue.

25. (New) The method of claim 7, wherein said cancer is breast cancer.

26. (New) The method of claim 7 or 18, wherein said cancer is prostate cancer.

27. (New) The method of claim 7, wherein said cancer is colon cancer.

28. (New) The method of claim 7, wherein said cancer is lung cancer.

29. (New) The method of claim 8, wherein said cancer is breast cancer.

30. (New) The method of claim 8, wherein said cancer is prostate cancer.

31. (New) The method of claim 8, wherein said cancer is colon cancer.

32. (New) The method of claim 8, wherein said cancer is lung cancer.

33. (New) The method of claim 19, wherein said cancer is breast cancer.

34. (New) The method of claim 19, wherein said cancer is prostate cancer.

35. (New) The method of claim 19, wherein said cancer is colon cancer.

36. (New) The method of claim 19, wherein said cancer is lung cancer.

37. (New) The method of claim 20, wherein said cancer is breast cancer.

38. (New) The method of claim 20, wherein said cancer is prostate cancer.

39. (New) The method of claim 20, wherein said cancer is colon cancer.

40. (New) The method of claim 20, wherein said cancer is lung cancer.

41. (New) The method of claim 21, wherein said cancer is breast cancer.

42 (New) The method of claim 21, wherein said cancer is prostate cancer.

43. (New) The method of claim 21, wherein said cancer is colon cancer.

44. (New) The method of claim 21, wherein said cancer is lung cancer.

45. (New) The method of claim 1, wherein said null IGF-I is selected from the group consisting of [Leu 60] IGF-I, [Ala31, Leu60] IGF-I; [Leu24, Leu60] IGF-I; [Leu24, Ala31, Leu60] IGF-I; [Leu24, 59, 60, Ala31] IGF-I; [1-27, Gly4, 38-70] IGF-I; [Ser24] IGF-I; [Leu24, 1-62] IGF-I and [1-29, gly, gly, gly, gly, 42-62] IGF-I.

46. (New) The method of claim 4, wherein said null IGF-I is selected from the group consisting of [Leu 60] IGF-I, [Ala31, Leu60] IGF-I; [Leu24, Leu60] IGF-I; [Leu24, Ala31, Leu60] IGF-I; [Leu24, 59, 60, Ala31] IGF-I; [1-27, Gly4, 38-70] IGF-I; [Ser24] IGF-I; [Leu24, 1-62] IGF-I and [1-29, gly, gly, gly, gly, 42-62] IGF-I.

47. (New) The method of claim 18, wherein said cancer is prostate cancer.